

Myocardial injury after phenylpropanolamine ingestion*

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SUMMARY Three patients developed clinical evidence of myocardial injury after acute ingestion of phenylpropanolamine, a sympathomimetic amine found in a large number of decongestant and appetite suppressant formulations. Increases in the serum creatine kinase and MB isoenzyme levels, ventricular arrhythmias, and electrocardiographic repolarisation abnormalities were seen. Excessive catecholamine stimulation has been shown to produce acute myocardial necrosis experimentally, and a similar mechanism may be present in these patients.

Phenylpropanolamine is a sympathomimetic amine used widely as a decongestant and appetite suppressant. It is freely available either over the counter or on prescription, usually in combination with other drugs. The effects of phenylpropanolamine are largely the result of alpha-adrenergic agonist activity resulting from both direct stimulation of adrenergic receptors and release of neuronal norepinephrine.¹ The principal adverse effect of phenylpropanolamine is dose related hypertension^{2,3} and ventricular arrhythmia has been described.⁴ Studies in rats have shown that sympathomimetic amines can cause myocardial necrosis,⁵ but evidence of this in humans after the acute ingestion of sympathomimetic amines has not been previously reported.

We describe three patients seen within four months who developed clinical evidence of myocardial injury after acute phenylpropanolamine ingestion, including an increase in the MB isoenzyme of creatine kinase and electrocardiographic abnormalities.

Case reports

CASE 1

A 24-year-old woman was admitted with chest pain three hours after ingesting a single capsule of phenylpropanolamine 50 mg, chlorpheniramine 4 mg, and belladonna alkaloids 0.2 mg. Dyspnoea, headache, blurred vision, and nausea were present. There was

no history of cardiovascular disease, hypertension, or ingestion of other drugs.

Blood pressure was 204/148 mmHg and pulse rate 112. She was confused and restless. The cardiovascular and respiratory systems and the fundi were normal. The initial electrocardiogram showed inferolateral ST segment depression. The chest x-ray film was normal and haemoglobin was 16.1 g/dl. Nitroprusside therapy promptly returned the blood pressure to normal and her symptoms resolved. Analysis of urine by thin layer chromatography disclosed phenylpropanolamine and chlorpheniramine, and this was confirmed by gas chromatography-mass spectrophotometry. The total serum creatine kinase level and MB isoenzyme fraction were high at 12 hours and had returned to normal 36 hours after drug ingestion (Table). The electrocardiographic ST-T abnormalities persisted for 48 hours and then returned to

Table Total serum creatine kinase (% MB fraction)*

	Admission	12 hours	24 hours	36 to 48 hours
Case 1	—	132 (2.5)	104 (11)	45 (<2)
Case 2	—	183 (6)	117 (2.5)	62 (<2)
Case 3	Normal	230 (2.5)	253 (<2)	67 (<2)

*Normals: creatine kinase 16-84 IU/l, MB fraction <2%.

normal. The subsequent course was uncomplicated and the blood pressure remained normal. Thyroid function tests, urinary metanephrine and vanillyl-mandelic acid levels, M-mode and two-dimensional echocardiograms, technetium pyrophosphate cardiac scintigraphic scan, and a submaximal graded exercise test were normal. Four months later the patient was asymptomatic and normotensive.

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CASE 2

An agitated 13-year-old girl was admitted with headache two hours after the deliberate ingestion of eight capsules each containing phenylpropanolamine 50 mg, chlorpheniramine 8 mg, and isopropamide 2.5 mg. There was no history of hypertension or cardiovascular disease, or of other drug ingestion. Blood pressure was 190/110 mmHg and pulse rate 120. The respiratory and cardiovascular systems and the optic fundi were normal. Capsule fragments were obtained after induced vomiting. Over the next hour the diastolic blood pressure rose to 150 mmHg. Intravenous hydralazine (20 mg) returned the blood pressure to normal within one hour.

The electrocardiogram showed inferolateral ST segment depression (Fig. 1A) and ventricular bigeminy which resolved spontaneously (Fig. 1C).

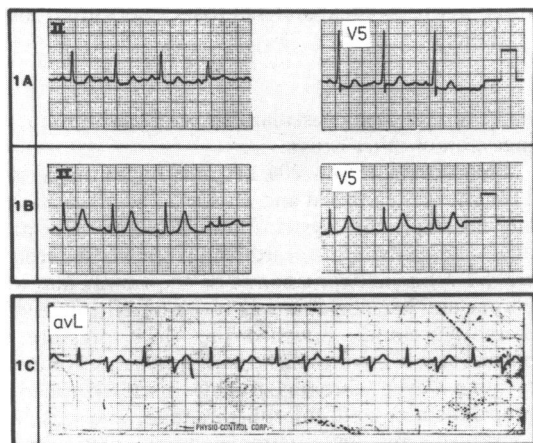


Fig. 1 (A) Electrocardiogram (leads II and V5) from case 2 at the time of admission. There is depression of the ST segment in both leads. (B) Twenty-four hours later, the repolarisation abnormalities have resolved. (C) Electrocardiographic rhythm strip (lead aVL) from case 2 in the emergency room showing ventricular bigeminy.

The chest x-ray film was normal. Analysis of urine showed phenylpropanolamine and chlorpheniramine. Total creatine kinase and the MB fraction were raised 12 and 24 hours after drug ingestion and subsequently returned to normal (Table). Quantitative chromatography confirmed the increase in the total creatine kinase and the MB isoenzyme. Electrocardiographic ST segment abnormalities resolved over 48 hours (Fig. 1B). Technetium pyrophosphate cardiac scintigraphy and M-mode and two-dimensional echocardiograms were normal. The subsequent course was uneventful and the patient was asymptomatic and normotensive two months after discharge.

CASE 3

A 31-year-old schizophrenic woman ingested approximately 40 tablets containing phenylpropanolamine 50 mg and caffeine 200 mg and began vomiting one hour later. There was no history of cardiovascular disease or hypertension. Medications included urecholine and trifluoperazine. The patient was agitated and the blood pressure was 180/120 mmHg, with a pulse rate of 90. Examination of the fundi, chest, and heart showed nothing abnormal. The chest x-ray film was normal, haemoglobin was 16.4 l/dl, and serum potassium 3.3 mmol/l. Analysis of urine disclosed phenylpropanolamine and caffeine.

The blood pressure returned to normal over three hours without treatment. The electrocardiogram was normal but an accelerated idioventricular rhythm developed (Fig. 2) for which lignocaine was given. Total creatine kinase and the MB fraction were nor-

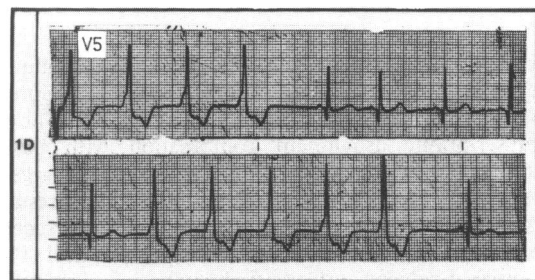


Fig. 2 Electrocardiographic rhythm strip (modified lead V5) from case 3 on admission to the intensive care unit showing an accelerated idioventricular rhythm.

mal on admission, raised 12 hours later, and had returned to normal at 36 hours (Table). No further rhythm disturbance was seen. M-mode and two-dimensional echocardiograms and technetium pyrophosphate scintigraphy were normal. One month after discharge the patient was normotensive and asymptomatic.

Methods

Creatine kinase was determined using a modification of Rosalki's method⁶ and its MB isoenzyme by electrophoresis. In case 2, determinations were also performed using quantitative chromatography on DEAE Sephadex A-50.⁷

Phenylpropanolamine was extracted from urine into an 80/20 mixture of chloroform/isopropyl alcohol and qualitatively assayed by gas chromatography-mass spectrophotometry. Phenylpropanolamine assay was also performed by thin layer chromatography.

Discussion

These cases illustrate that enzymatic and electrocardiographic evidence of myocardial injury may occur in young, healthy patients after phenylpropanolamine ingestion. Electrocardiographic repolarisation changes, ventricular arrhythmias, and clinical symptoms suggest that this myocardial injury may have important consequences, and each of our patients required monitoring in an intensive care unit. The initial patient, who had chest pain, high creatine kinase levels, and electrocardiographic abnormalities admitted taking only 50 mg of the drug. Though the patient was judged reliable, quantitative determination of phenylpropanolamine was not obtained. While it is thus possible that therapeutic doses of phenylpropanolamine have the potential for producing myocardial toxicity in certain patients, we cannot say this conclusively in our patient. The recognition of myocardial injury in two successive patients with intentional overdoses of phenylpropanolamine suggests, however, that this may be a common complication of excessive phenylpropanolamine ingestion.

Histological evidence of diffuse focal myocardial necrosis has been produced in animals by both sympathomimetic amines and catecholamines.^{8,9} Infusions of noradrenaline or isoprenaline as brief as six hours can produce such lesions.¹⁰ While the effects of phenylpropanolamine have not been studied, a variety of similar sympathomimetic amines have been shown to produce microscopical lesions of myocardial necrosis in rats.⁵ Studies of patients with pheochromocytoma have shown that prolonged excessive catecholamine stimulation is associated with similar myocardial lesions in humans,¹¹ and case reports of myocardial necrosis following infusions of noradrenaline given for only a few days suggest that such injury may also occur more acutely.¹²

These studies in both animals and humans indicate that excessive adrenergic stimulation can cause myocardial necrosis. Since phenylpropanolamine is a direct adrenergic agonist and also releases endogenous catecholamines, it is likely that it caused myocardial injury in our patients by this mechanism. Though there is a report of cardiomyopathy in a chronic amphetamine abuser,¹³ we are not aware of previous reports of acute sympathomimetic ingestion resulting in either histological or clinical evidence of myocardial injury.

The way in which adrenergic stimulation could cause myocardial necrosis is unclear. Alpha-adrenergic mediated coronary vasoconstriction has been well documented in dogs,¹⁴ but the ability of the pure beta-adrenergic agonist isoprenaline to produce myocardial necrosis⁹ argues against this possibility. It is also unlikely that a primary increase in myocardial

oxygen consumption secondary to hypertension and mild tachycardia resulted in myocardial ischaemia in our patients. Each was a young woman with no history of coronary artery disease or hypertension and no electrocardiographic or echocardiographic evidence of left ventricular hypertrophy. Histological studies of dogs given noradrenaline infusions to produce myocardial necrosis have shown increased platelet aggregates in myocardial capillaries. Pretreatment with antiplatelet agents reduces both the aggregates and the degree of myocardial necrosis.^{15,16} Capillary occlusion by circulating platelet aggregates is thus a possible mechanism for myocardial injury.

While the formulations ingested by each of our patients contained additional drugs, the only agent common to all three patients was phenylpropanolamine. These additional drugs were pharmacologically dissimilar (chlorpheniramine, caffeine), and it is unlikely that they were the primary cause of myocardial injury. It is possible, however, that they contributed to the phenylpropanolamine toxicity. Caffeine increases plasma catecholamine levels¹⁷ and chlorpheniramine inhibits neuronal reuptake of catecholamines.¹⁸

This report shows that clinical evidence of myocardial injury may result from the ingestion of excessive doses of phenylpropanolamine. While therapeutic doses may also cause such toxicity in certain subjects, this cannot be clearly established from our observations. Documentation of the incidence and relation of this adverse effect to drug dosage is needed because of the widespread availability of phenylpropanolamine.

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